CLINICAL AND EXPERIMENTAL EXPERIENCE WITH COLLOIDAL SILVER AND A VIRULENT STREPTOCOCCUS.[1]

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Any means by which one can cope successfully with a severe streptococcic infection, or prevent it, is of interest alike to the internist, surgeon, and obstetrician, because of the ubiquity of this organism, its protean manifestations, and its death-dealing properties. The internist now knows it is responsible for many cases of pleurisy, meningitis, acute articular rheumatism, suppurative arthritis, double parotiditis, hematuria, bronchopneumonia, enterocolitis, etc., though not always able to distinguish clinically those instances in which it is the etiological factor. To the surgeon and obstetrician it is only too well known as playing a large part in all wound complications, but fortunately their aseptic methods have curtailed its ravages. Colloidal silver is a remedy which has received much attention during the past three or four years. An impartial perusal of its literature cannot fail to impress one with its value in various infections, not only those due to the streptococcus, but to the staphylococcus, pneumococcus, anthrax bacillus, etc.

An allotropic form of silver was first described by Carey Lea in 1880,[1] but remained simply a laboratory curiosity until 1897, when introduced into surgical practice by Credé, of Dresden, in a paper read before the Twelfth International Medical Congress at Moskow. Credé had been lead to an inquiry into the therapeutic value of silver and its salts through observation of his father's well-known predilection for nitrate of silver in the treatment of ophthalmia, and also by his early recognition of the shortcomings of iodoform and mercurial preparations in wound treatment.

Nitrate of silver proved entirely unsatisfactory in the treatment of wounds, because of its ready decomposition and caustic action. Various albuminates were then tried, but his investigations were without result until Halsted's method of dressing wounds with silver-foil was witnessed. Following up this cue he found that metallic silver placed in aseptic wounds remained unchanged and was non-irritating, but when covering septic wounds, or a culture of one of the pyogenic cocci, the silver-foil disappeared, was dissolved—and in the Petri dish the silver was surrounded by a sterile zone. The only explanation was that the products of bacterial growth built up soluble antiseptic combinations with the silver. Chemical examination of the sterile zone surrounding the silver-foil in the culture medium corroborated this hypothesis and demonstrated the lactate to be the principal compound thus formed. Experiments with the lactate and about twenty other organic salts of silver finally proved the citrate the most suitable for surgical purposes, and since then Credé has employed the citrate of silver with extreme satisfaction in the treatment of all wounds—for irrigation, impregnation of dressings, and for the sterilization of catgut.

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[1] Read at a meeting of the Medical Society of the District of Columbia, Washington, April 11, 1906.

[2] Silliman's Journal of Science, third series, vol. xxxvi, p. 477.

As the result of this success the idea suggested itself that, as under the influence of pyogenic cocci antiseptic salts were formed from silver, perhaps it would be possible to bring about a disinfection, so to speak, of the entire body, if silver could be brought directly into the blood and body fluids, which would, of course, necessitate a form of metallic silver soluble therein. After consultation with many competent chemists, von Heyden produced a colloidal silver which, though not perfectly soluble, was applicable in following up this idea.

This preparation consists of small black particles of metallic luster, easily crushed, and containing 92 to 98 per cent. of silver; it is inodorous and almost tasteless. It is soluble in one to twenty parts of water; strictly speaking, however, it is not a solution, for the silver is merely in suspension, in particles so fine as hardly to be seen with the microscope; it filters through paper, but not through animal membranes.

At first it was employed chiefly in the form of a 15 per cent. ointment by inunction. It was rather irritating for hypodermic use. In the presence of a 1 per cent. egg albumen the silver is not precipitated by salts and acids, and in this combination has been administered by the mouth. In exceptionally severe cases Credé thought it might be given intravenously as bichloride of mercury was then being used by Bacelli, though at that time he had not thus employed it. Its intravenous use was taken up first at the Veterinary High School, Berlin, by Prof. Dieckerhof, and later by other veterinarians, and thus was successfully employed in the treatment of sepsis and various infectious diseases of cattle. Feeling thus relieved of the necessity of animal experimentation by its success in veterinary practice, Credé has employed colloidal silver by intravenous injection, since 1898, in the treatment of sepsis, pyemia, acute articular rheumatism, advanced pulmonary tuberculosis, and many other conditions, in doses of 5 to 20 c.c. of a 0.5 to 1 per cent. solution.[1]

My interest in colloidal silver, its value and limitations, especially when given intravenously, was aroused by the results noted in a most serious streptococcic infection seen in 1905. I had used it by inunction in the previous several years in a variety of affections, among them instances of streptococcic infection, and uniformly with gratifying success, so I that was unprepared for the temporary failure which attended my efforts in this case.

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[1] Berl. klin. Woch., September 16, 1901, p. 941.

On July 5, I was called to see a young man, aged nineteen years. For two days he had been feeling a little below par. His nose was slightly swollen, but that fact was not complained of, nor had it been scarcely noticed; his temperature was 102°. The condition was readily recognized as a facial erysipelas. I ordered the liberal application of Credé ointment to the nose and face, fully expecting, and in fact confidently predicting, a prompt cure. Perhaps this might have been the result had it not been for his indiscretion in getting out of bed the next morning, as he felt perfectly well. About three hours later I was hurriedly sent for, and found him suffering with a violent epigastric pain. The abdomen was quite soft, and my attention was immediately directed to the chest by his sighing respirations and tumultuous heart action. The lungs were normally resonant, but there was a pleuritic friction rub below the right nipple, and a blowing murmur at the apex of the heart; temperature, 104°. The streptococcus was evidently exercising its predilection for serous surfaces, as shown by the beginning pleurisy and endocarditis. An ice-bag was placed on the precordium, and during the next forty-eight hours Credé ointment was applied freely by inunction over the entire chest and abdomen.

On the evening of the third day it was apparent the infection was gaining the upper hand: an effusion had developed in the right pleural cavity; the heart action was more tumultuous, the blowing murmur at the apex louder; temperature, 104.6°. During the next twenty-four hours he was given five intravenous injections of 5 c.c. each of a 1 per cent. solution of colloidal silver, and one tub bath, at 80° F., of twelve minutes' duration: with the result that the apical murmur disappeared entirely, the heart action greatly improved, and the pleuritic exudation diminished considerably.

But at 10 P.M. on the fourth day, in spite of one-fourth gram of colloidal silver thus administered intravenously, his temperature was 105°; pulse, 100; respirations, 34; over the entire posterior aspect of both lungs were crepitant rales, impaired resonance, and increased vocal fremitus. Still more disheartening, not only had the swelling of the nose extended to the cheeks and scalp, but an entirely new focus of erysipelas, an area the size of the palm of the hand, had appeared on the calf of the left leg, at the site of an insect bite received in the woods a few days before the beginning of his illness. Extending from this new area up the leg to the knee were three parallel red streaks, looking like scratch marks, and indicating the course of inflamed lymphatic channels. A second bath of the same duration and temperature was given and a sixth intravenous injection, this time 10 c.c. of a 1 per cent. solution.

The morning of the fifth day the temperature dropped to 103.2°, respirations to 25, pulse to 80; the lungs were normally resonant posteriorly where there had been beginning consolidation the night before. But at 4 P.M. the temperature was 105° in spite of the subsidence of the alarming chest symptoms; the new erysipelatous area on the leg had greatly increased in size, the entire leg was swollen, and the lymphangitis had extended to the groin; the urine was loaded with albumin and contained a few granular casts. The intravenous injection of colloidal silver was increased to 5 c.c. of a 5 per cent. solution, this amount being repeated at midnight and twice the next day. That ended the intravenous injections, for every available vein had been used until none could be entered again with the needle, by reason of considerable swelling of the arms in consequence of the escape into the tissues of some of the solution during attempts at injection into the smaller veins.

During ninety-six hours the patient received 1.5 grams of colloidal silver intravenously, 1 gram being injected during the last twenty-four hours of that period. The backbone of the attack was broken by this large dose of 1 gram intravenously inside of twenty-four hours, for on the evening of the sixth day, at the time of the last intravenous injection, the temperature had dropped to 102.2°, and the condition of the leg was rapidly improving. Had this large dose been employed from the start, or had I been able to continue it a short time longer, I believe this would have been the end of the attack.

The inunctions were continued, the face, entire front of the chest and abdomen, and the entire left leg being continually covered with the ointment and enveloped with oiled silk, as much as thirty grams a day being thus applied; this I supposed, of course, would be sufficient to maintain the good effects obtained by the intravenous injections. But in this I was to be disappointed, for on the evening of the eighth day, forty-eight hours after the last intravenous injection, the temperature again showed a tendency to rise, and the erysipelatous areas again began to extend.

Rectal injections of colloidal silver were resorted to, but did not control the smouldering embers of the infection until the dose was increased from 0.5 gram to 2 grams three times a day. For the next ten days, that is from the eighth to the eighteenth day of the disease, the temperature continued between 102° and 103°; but the morning of the eighteenth day it was so near normal that the rectal injection was reduced to 1 gram, and so continued until the twenty-first day, when symptoms appeared which indicated the limit had been reached in the administration of colloidal silver. Fortunately, it was no longer needed, for on the evening of the twentieth day the temperature was for the first time normal. By the rectum the patient had received 50 grams of colloidal silver; by the skin it is impossible to say how much was absorbed, but about 500 grams of a 15 per cent. ointment was used.

During the thirteen days of rectal injections the erysipelas cleared on the face, after extending to the ears and well into the scalp. When the face had appeared quite normal for several days, the application of the ointment to the face was discontinued. Within forty-eight hours the lips and nose again began to swell, and though the inflammatory process was much less marked than in the primary attack, a dusky redness spread not only over the entire scalp, but this time down the neck, over the entire back and left arm, over the right shoulder and entire front of the chest, with here and there an angry patch the size of the palm of the hand. During this same period of rectal injections the focus on the leg extended below to the dorsum of the foot, where the swelling and inflammation were particularly severe, and above to the middle of the thigh, so that the only part of the entire cutaneous surface not involved at one time or another was the right arm and leg, the upper part of the left thigh, the buttocks, and in front the abdomen. It was found that after the migrating inflammation had passed a given point, and though for several days the skin had appeared normal, the inflammatory process would again flare up if the local silver application was discontinued, so that at one time about two-thirds of the body was covered with the ointment. In fact, after the temperature had been normal for a week, that is nearly a month from the beginning of the disease, the ointment was again left off the face, and again for the third time the lips and chin began to swell, and coincidently a new area of erysipelas appeared over the right trochanter; but both areas quickly subsided on the application of the ointment, and the temperature did not rise.

I was constantly on the lookout for some symptom indicating the limit had been reached in the administration of these large amounts of silver. The sclerotics had a peculiar blue tint suggesting the presence of a silver deposit in all the tissues. On the nineteenth day of the disease some pain in the stomach was complained of; and on the twentieth there was considerable vomiting of a watery fluid of such a gray tint as to suggest the presence of metallic silver, though none had been taken by the mouth. A specimen of the vomitus was examined by Dr. E. R. Hodge and found to contain silver. The gastric pain and vomiting soon disappeared on stopping the rectal injections.

The boy's troubles were not all over with the disappearance of the fever. During the next three weeks, that is from the twenty-first to the fortieth day, thirteen large abscesses formed in the left leg and arm, from which about two liters of pus was evacuated, containing as it was ascertained, the streptococcus in pure culture. In the left foot the inflammatory process reached almost the stage of gangrene; a four-inch incision on the dorsum disclosed a subcutaneous slough the size of the hand, and a second incision of two inches along the tendo Achillis showed a black necrotic area the size of a silver dollar. Most of the abscesses formed very rapidly, practically with no local reaction; one or two hundred cubic centimeters of pus would be evacuated and the abscess cavity would close up in a most remarkable manner in three or four dressings. Two months after the subsidence of the fever, and when convalescence was nearly complete, the virulent streptococcus gave him a parting stab in the form of a small axillary abscess. It is needless to say his convalescence was very tedious; he was far more emaciated than any typhoid patient I have ever seen.

On the twenty-second day of the disease I was called about three o'clock in the morning, and found the patient in a state of collapse which nearly proved fatal; temperature 95° per rectum, breath and extremities cold, no pulse, and heart action barely audible. Hot salt solution per rectum with adrenalin brought a prompt response, though it had to be repeated several times to meet a recurrence of these symptoms. This collapse was evidently precipitated by the loss of fluids to the tissues incident to the copious vomiting of the previous twenty-four hours; and for a week fluids had to be administered freely to prevent a threatened recurrence.

The left arm could not be used for weeks. At one time it was so thin, the skin so tightly drawn over it, the biceps muscle so indurated, as to remind one of a well-dried part in the dissecting-room.

That the colloidal silver was to be credited with the cure of this patient was the unavoidable impression made upon me in watching it. Locally applied the silver exerted a most important local influence, for repeatedly when its local use was discontinued the inflammatory process in the skin flared up in areas which had apparently recovered completely some time before. The rectal injection, increased to 9 grams a day, finally overcame the remnants of the infection, but only after the backbone of the disease had been broken by the intravenous injection of 1 gram within a space of twenty-four hours—0.5 gram intravenously, extended over a period of seventy-two hours, having proved ineffectual.

Accumulated experience has proved conclusively the value of colloidal silver in combating various infections, both in the lower animals and in human practice, but it would extend this paper far beyond reasonable limits to attempt to review it. I now desire to turn to another phase of the application of colloidal silver, that is the question of its prophylactic value, concerning which there is but meager clinical and experimental data. Having in my possession, from this case, a virulent streptococcus which had been successfully combated, as just related, I undertook a few experiments on rabbits, with a view to obtaining further impressions as to its value and limitations in preventing infection by this same organism.

It was most natural for Credé to endeavor to extend the application of colloidal silver to the prevention of infection.[1] In recommending the insertion of suitable suppositories in the uterus and vagina after childbirth, he was simply making use of its local bactericidal effect. That was undoubtedly also his idea in leaving two or four tablets in the abdominal cavity after intestinal resection and similar operations especially likely to be followed by infection; the tablets were composed of 0.05 gram of colloidal silver rubbed up with a like amount of sugar of milk, so as to be readily soluble, and as many as ten tablets, he thought, might thus be allowed to remain in the peritoneal cavity. In fact, however, in addition to the bactericidal effect of the silver, he was unwittingly taking advantage of a property of the peritoneum which has only recently been the subject of laboratory inquiry, and hardly yet applied clinically: I refer to the local immunity acquired by the peritoneum against infection as the result of a passing irritation, it having been found that intraperitoneal injections of salt solution, urine, (2 per cent.), nucleic acid, boullion, blood serum, etc., so increases the resisting powers of the peritoneum that many times a lethal dose of various micro-organisms can be injected into its cavity, twenty-four hours later, without any effect.[1]

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[1] Monatsschr. f. Geburtshülfe und Gynäkologie, December, 1898, p. 583.

A further natural extension of these efforts at prophylaxis, and the outcome of his success in treating various infections, once established, was Credé's advice to give colloidal silver intravenously, during or following all septic operations, just as many surgeons give a saline transfusion.[2] In support of this departure he might have invoked the experience of Ewers in veterinary practice, though unique, I believe, in preventing by intravenous injection of colloidal silver a fatal dysentery which is endemic on some farms and attacks calves in the first days of life. The only experimental evidence I have been able to find favorable to colloidal silver is that of Beyer,[3] an assistant of Credé, which, however, is along the line of clinical and veterinary experience as to its value in combatting various infections once established, though in itself not conclusive, as but two dogs were used, and no control.[4] The only other experiments bearing in any way on the value of colloidal silver, either in combating or preventing infection, in which the small laboratory animals were employed, are those of Brünner, Trommsdorf and Cohn—all equally unsuccessful in demonstrating any virtue in prophylactic injections of colloidal silver against inoculation with various microorganisms.

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[1] Issaeff, Zeit. f. Hygiene, 1894, p. 287; Borchard, Deut. med. Woch., 1904, No. 49; Miyake, Mitteilungen aus den Grenzgebieten der Med. u. Chir., 1904, xiii, p. 179; Petit, Ann. de l'Inst. Pasteur, 1904, xviii, 407; Durham, Medico-Chir. Trans., London, 1897, lxxx, 191; Mikulicz, Lancet, July 2, 1904, p. 1.

[2] Archiv. f. klin. Chir., 1903, xlix, 225.

[3] Münch. med. Woch., 1902, No. 8, p. 331.

[4] One dog was given intravenously 10 c.c. of a virulent staphylococcus culture. Twenty-eight hours later the animal was getting progressively worse; it then received 0.4 gram of colloidal silver, with prompt recovery, the temperature reaching normal on the fifth day. In a second dog he obtained the same favorable result from a similar dose subcutaneously, but the fever lasted ten days and the effect of the treatment was not so striking.

The article of Brünner[1] is much quoted, but only four of his experiments concern this aspect of the subject. In only one of them was the result favorable to colloidal silver: 1.50 of a staphylococcus culture was given a small dog intravenously, and a half hour later 0.1 gram of colloidal silver—the animal living seven and one-half days, while the control lived but eighteen hours. But in a second experiment a larger amount of the staphylococcus culture was injected and the animal died in seven and one-half hours, while the control lived. In the two remaining experiments the animals receiving the colloidal silver died as soon as the controls.

In the experiments of Trommsdorf[2] twelve dogs were given intravenous injections of colloidal silver varying from 0.02 to 0.03 gram, which in proportion to weight is about ten times the amount recommended by Credé as a prophylactic in human practice. Six, twelve, twenty-four, and thirty-six hours later a culture of the organism of swine erysipelas was injected intravenously—all the animals dying as soon as the controls.

The experiments of Cohn[3] are the most exhaustive. In two of them the cholera spirillum was the infecting organism: a guinea-pig receiving an intraperitoneal injection of a bouillon culture, followed by 0.05 gram of colloidal silver, lived four hours longer than the control; but a second guinea-pig died in twenty-four hours and the control lived. In four experiments with anthrax injected intravenously, followed by colloidal silver in dose of about 0.1 gram per kilo of animal weight, all the controls lived the longer. In two of four experiments with the staphylococcus injected intravenously the results were slightly in favor of the animals receiving the colloidal silver.

It will be observed that in these experiments, with the exception of two intraperitoneal inoculations, the infecting organism was thrown directly into the circulation, in relatively overwhelming numbers. This method of inoculation in no way simulates the manner of acquiring disease through the ordinary channels of infection, when the invading organism gains access to the circulation late in the course of the disease, or frequently not at all. In experiments with the streptococcus, however, three in number, Cohn inoculated the scarified ear of a dog with a loopful of the culture, followed by an intravenous injection of colloidal silver, about 0.1 gram per kilo of animal weight, and in each instance the control lived the longer.

But in these last mentioned experiments of Cohn the colloidal silver was injected at the time of the inoculation with the streptococcus. Now the leukocytosis following the administration of colloidal silver, which is at its height at the end of twenty-four hours, plays an important, but as yet imperfectly understood, part in its action. It has been shown[1] in efforts at the prevention of infection through a hyperleukocytosis induced by the injection of nuclein, peptones, albumoses, and other substances, that to obtain favorable results it is necessary that the inoculation be made at the height of the induced leukocytosis. It was with the idea of filling up this small lacuna that I undertook the experiments mentioned, inoculating twenty rabbits subcutaneously twenty-four hours after the injection of colloidal silver, when the leukocytosis was at its height.

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[1] Fortschr. d. Medizin, May 16, 1900, p. 381.

[2] Münch. med. Woch., August 5, 1902, p. 1300.

[3] Centralb. f. Bacteriologie, 1902, vol. xxxii, p. 732.

Twenty-four hours after an intravenous injection of colloidal silver the average leukocytosis was 12,000, due chiefly to an increase in the polynuclear cells; after intraperitoneal injections the leukocytosis was of about the same intensity, but due chiefly to an increase in the lymphocytes, as if the entire army of polynuclear phagocytes had responded to the local call in the peritoneal cavity. The degree of leukocytosis bore no relation to the amount of colloidal silver injected.

The streptococcus had been kept for a month without transplantation, yet it was found that 5 c.c. of a twenty-four-hour culture killed two-months'-old rabbits in about eighteen hours, when the inoculation was intravenous. The organism was peculiarly capable of surviving unfavorable conditions for growth, as it was successfully transplanted from an almost dry agar tube at the end of three months.

The colloidal silver was administered in some instances subcutaneously, and in others into the peritoneal cavity or intravenously, the dose varying from 0.003 to 0.500 gram per kilo of animal weight, in 0.5 to 5 per cent. solution.[2] The result of these prophylactic injections can be told in a few words. In no instance was a local reaction from the subcutaneous inoculation with the streptococcus entirely prevented, but with the largest dose of 0.5 gram per kilo of animal weight the inflammatory process was transitory and in marked contrast to that excited in the control. As the result of a particularly severe local reaction in a rabbit receiving intravenously 0.003 gram per kilo, I had my attention directed to the possibility of these smaller doses lessening the animal's resisting powers. In support of this idea it was repeatedly noted that the inflammatory reaction was much greater in animals given a previous small intraperitoneal injection of colloidal silver. Moreover, one rabbit was so far immunized by repeated small doses of the streptococcus as twice to have no local reaction, but when again inoculated twenty-four hours after a subcutaneous injection of colloidal silver, 0.004 gram per kilo, the usual erysipelatous inflammation appeared. All the controls lived, while two of the animals receiving small doses of colloidal silver and inoculated as related, twenty-four hours later with the streptococcus, died: in one, the dose was 0.070 gram per kilo subcutaneously, and in the other, 0.030 gram per kilo intravenously.

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[1] Labbé, La Presse medicale, July 18, 1903, p. 519.

[2] In one rabbit the largest dose of 7 c.c. of a 5 per cent. solution was fatal when injected into a vein as rapidly as the syringe could be emptied. There were two or three convulsive movements, respirations ceased, the heart action continuing about three minutes. Postmortem: the left ventricle was found empty, while the right side of the heart and all the large veins were distended with a continuous blood-clot; the lungs were compressed against the back of the thorax, dark in color, and perfectly dry on section. The rapidity of the injection was a factor in producing this death, for a similar injection in another rabbit, given very slowly, was apparently without ill effect.

Of course, these experiments do not permit of any broad generalizations, but taken in connection with those of Brünner, Trommsdorf, and Cohn, they at least suggest—in spite of the well-demonstrated value of colloidal silver against infection once established—that in doses heretofore advocated, no confidence can be placed in its ability to prevent infection; and they further suggest these small doses may even lessen the patient's resisting powers, whether used intravenously, in the peritoneal cavity, or subcutaneously, and actually be an added source of danger.

A NOTE ON THE PRODUCTION OF VASCULAR LESIONS IN THE RABBIT BY SINGLE INJECTIONS OF ADRENALIN.[1]

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The many publications which have followed Josué's demonstration of the power of adrenalin to produce degenerative changes in the rabbit's aorta have added much to our knowledge of the degenerative, infiltrative, and reparative processes which may occur in bloodvessels; but, unfortunately, from the point of view of comparative pathology, the value of this method of experimentation has been lessened by the failure to produce lesions entirely analogous to those of arteriosclerosis in man—the condition which it most closely resembles, and further, by the absence of an adequate explanation of the manner in which adrenalin acts to produce such lesions.

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[1] Read at the meeting of the Association of American Physicians, Washington, D. C., May 15 and 16, 1906. This work was conducted under a grant from the Rockefeller Institute for Medical Research.